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Date: July 21, 1977

Project Title: Georgia Heart Association Investigatorship in the Field of Cardiovascular Disease

Project No: E-23-629

Project Director: Dr. Hyland Yu-Liang Chen

Sponsor: Georgia Heart Association, Inc.

Agreement Period: From 7/1/77 Until 6/30/78

Type Agreement: Letter Agreement dated May 24, 1977

Amount: $10,000

Reports Required: Annual Progress Report

Sponsor Contact Person (s):

Technical Matters

Contractual Matters (thru OCA)

Dr. Joseph A. Wilber
President
Georgia Heart Association, Inc.
Broadview Plaza, Level "C"
2581 Piedmont Road, N.E.
Atlanta, GA 30324
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Defense Priority Rating: N/A

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SPONSORED PROJECT TERMINATION

Date: 12/4/78

Project Title: Georgia Heart Association Investigatorship in the Field of Cardiovascular Disease

Project No: E-23-629

Project Director: Dr. Hyland Yu-Liang Chen

Sponsor: Georgia Heart Association, Inc.

Effective Termination Date: 6/30/78

Clearance of Accounting Charges: 6/30/78

Grant/Contract Closeout Actions Remaining: NONE

- _ Final Invoice and Closing Documents
- _ Final Fiscal Report
- _ Final Report of Inventions
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- _ Other ____________

NOTE: Continued by E-23-639

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E-23-629

PROGRESS REPORT

GHA Investigatorship

I. Investigator

Hyland Yu-Liang Chen, Ph.D.
Engineering Science and Mechanics
Atlanta, Georgia 30332

July 1, 1977 to June 30, 1978

II. Major Research Projects

1. Instrumentation

A. Development and construction of the experimental system of muscle mechanics

The system has been evolved over the years from a dynamic muscle puller with 5 milisecond rise time (see proposal to GHA, 1973) to a system consisting of four subsystems, i.e., environmental, mechanical, optical and control subsystems (see proposal to NSF, 1977).

The design of the system is completed. The construction had been underway since 1976 with institutional funds as well as funding from NSF Initiation Grant and GHA Grant-in-aid. The last NSF Grant of $38,500 (1977) provided the funds to complete the development. When the system is completed in December 1978, it will have a multimicroprocessored control and monitoring system (completed), a mechanical system of 150 microsecond rise time, comparable with the state of art, e.g., 400 microsecond of A. Huxley's and 200 microsecond of Lincoln Ford's (completed), and an optical system of two laser beams for measurements of sarcomere length and electric activities (under construction). The system will be usable for studies on heart muscle, skeletal muscle and muscle fiber. The utilization of the system by the colleges of Georgia is solicited.

Please note, the development of a state of art experimental system is the first step toward quantitative study of heart muscle mechanics.

B. Development and construction of Alphatron:

A one dimensional testing device for polymeric materials and soft tissues as well as arterial smooth muscle.

The Alphatron is a multimicroprocessor controlled and monitored system capable of performing standard testing routines on soft tissues and polymeric materials, i.e., creep, relaxation and simple elongation at variable rates, as well as the classical testing routines on smooth muscle, i.e., isometric, isotonic, quick release and quick stretch. Actually, the operation of the Alphatron is software oriented. New tests as well as sequential combinations of classical tests can be programmed and thus performed. Via a keyboard, the experimentalist can communicate with the Alphatron by short orders in English. The era of button pushing is ended as regards this machine. The data of a test is automatically monitored and stored in the memory in digital form, as well as being graphically displayed.

The Alphatron has been completed last spring after three and half years of development with institutional funds.

The system is suitable for studies in mechanics of smooth muscle and other soft tissues. The utilization of this system by colleagues of Georgia is solicited.

2. A Quantitative Study of the Mechanical Behavior of Endopelvic Fascia

In order to understand the physiological function of an organ or tissue, it is often necessary to obtain information about its mechanical properties. Recently, medical research in pelvic relaxation has established the need for mechanical data on the behavior of tissues in the female pelvic support structures.

Pelvic relaxation is a general term used to describe all conditions in which the supporting structure in the female pelvis no longer maintains the organs in their normal position. It is usually found in older women. Most procedures for surgical repair of these conditions are based on the theory that there is a generalized relaxation, or attenuation of the connective tissues comprising the pelvic supports. Surgical repair is needed when extensive stretching leads to herniation or the disruption of the normal functions of the pelvic organs. General application techniques to shorten the "elongated" pelvic supports are commonly used.

While pelvic relaxation is "among the commonest complaints heard daily by all gynecologists . . . . successful vaginal repair is the most difficult type of gynecologic surgery, and even an experienced gynecologist may have failure rates ranging from 25 to 41 percent." [1] These failure rates are observed to increase with time.

Research in the clinic of Dr. A. C. Richardson of Atlanta has led him to conclude that usually, if not always, pelvic relaxation is the result of an isolated defect or tear in the pelvic support tissues rather than a generalized stretching. Between January 1971 and October 1975, 93 operations were performed in which localized defects were found and repaired. Their failure rate was less than 5%. In addition, three of the four failures were evident within six weeks after surgery [2].

In order to analyze the genesis of pelvic relaxation, the following questions need to be answered:

(1) Which structures provide support for the pelvic organs?
(2) What is the geometric configuration of these structures?
(3) What are the loads on these structures?

(4) What are the mechanical properties of the tissues comprising the pelvic supports?
(5) What is the histology of these tissues?

A pilot study has been initiated to study the anatomy of the pelvic supports and the histology of the tissues involved. Preliminary results indicate that several structures provide support for the pelvic organs. Histological studies [3] have shown that endopelvic fascia has a large percentage (over 50%) of smooth muscle. Smooth muscle was found to be predominant in every structure extending from the uterus to the pelvic sidewall.

The purpose of this work was to test specimens of endopelvic fascia to obtain information about the mechanical properties of various tissues in the pelvic support structure. Tissue samples obtained in longitudinal and latitudinal strips were tested in order to observe possible anisotropic behavior. Samples from various sites were tested in order to observe any variation with respect to location in the structure.

Data had been accumulated for 8 autopsy materials. Analysis procedures for the data reduction are completed. Experimental system has been constructed. We are patiently waiting for autopsy material--research in Bioengineering can be macabre sometimes.

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1. Baden, Wayne F., Ed., "Vaginal Relaxation", Clinical Obstetrics and Gynecology, 15, 1033, 1972.

2. Richardson, A. C., Lyon, J. B. and Williams, N. L., "A New Look at Pelvic Relaxation." Am. J. of Obstetrics and Gynecology, 126:568, 1976.

3. Richardson, A. C., Shemlock, B. and Williams, N. L., "Pelvic Supports, Dynamic Structures?" (In press).

3. Birefringence Studies in Muscle Fiber--An Optic Probe of Muscle Ultra-Structure

The birefringent properties of muscle have been known since the 19th century (Bozler & Cottrell, 1937), and in the 1930's and '40's birefringence studies were seen as a potentially productive way of studying ultrastructural changes in muscle during contraction. The advent of the more elegant techniques of x-ray diffraction analysis and electron microscopy pushed birefringence aside for a time (Fischer, 1947), but recently it has once again been used, with greatly improved technique (e.g., Taylor, 1976), as a nondestructive tool for studying muscle contraction.

However, up to date, the experimental methods can not resolve the true birefringence signal from either the noise of light source or the change of transparency of muscle due to activation (D. K. Hill, 1952); the birefringence has been observed as an isolated uncorrelated phenomenon; and a theory of muscular contraction to correlate the optical phenomena quantitatively with mechanical response and other properties of the muscle is wanting.

In the course of searching for a technique that measures muscle length sans damaged-end artifact, the applicant saw laser beam had been used in the sense of illumination (Hefner & Donald, Univ. of Ala., Private Communication), and in the sense of Fourier optics (G. Pollack, Univ. of Wash., Private Communication). Naturally, the question, "What can one see, if one regards the light beam as a electromagnetic field propagation?" arose. The answer was: by the interplay of the electric activities and micromolecules of muscle, a linearly polarized light will be partially depolarized, hence one can have a optic probe for the electric activity of muscle.

As reported by Baylor et al, electric activities of muscle are compartmentalized. To eliminate ambiguity, we proposed to study the cross bridge properties using triton-extracted, glycerinated rabbit psoas muscle fibers.

Our work on this problem so far has been: a rigorous analysis of the light propagation as EM field on all the experimental systems and experiments in literature; based on the analysis, a theoretical derivation of a method of birefringence measurement; an instrumentation design; and a partial realization of the system. The design of the new method of birefringence measurement was based on our derivation of the field transformed by different arrangements of the optic components and our study of the problems encountered by other experimenters. An instrument has been in part realized. The realization so far includes a laser, the optics necessary to control the polarization, focusing and analysis of the beam, and the muscle puller.

The proposed optic probe is designed to have a minimum frequency response of 20 K H_z; also it has the ability to differentiate signal of <u>true</u> birefringence from artifacts, such as light scattering due to muscle activation and light source noises. Thus, it would allow us to attempt dynamic time course study of cross bridge activities in intact musclar contractures. Conventionally, the studies of the cross bridges are carried out by mechanical and biochemical studies, and x-ray diffraction techniques. The mechanical studies are limited to 1 kH_z by the speed of the puller, the structural stability of the muscle fiber, and the frequency response of transducer. The x-ray technique is limited by the complexity of the data; hence, it is relatively difficult to perform a dynamic time course study such as quick release and quick stretch. As for biochemical studies, it is usually required to break up the muscular contracture. Hence, it seems that the proposed system can cover the area of high frequency, dynamic time course study of cross bridge activities in intact muscularcontracture. There are interesting phenomena to be studied, such as, characteristic time of cross bridge attachment and detachment in intact muscle and by established analysis such as relaxation process in high polymer physics, to deduce the physical characteristics of the cross bridges.

References

1. Bozler, E., and C. L. Cottrell. 1937. The birefringence of muscle and its variation during contraction. J. Cell. Comp. Physiol. 10, 165-182

2. Hill, D. K. 1952. The effect of stimulation on the diffraction of light by striated muscle. 119, 501:

3. Taylor, D. L. 1976. Quantitative studies on the polarization optical properties of striated muscle. I. Birefrigence changes of rabbit psoas muscle in transition from rigor to relaxed state. J. Cell. Biol. 68, 497-511

4. Baylor, S. M. and Oetliker, H. 1976. A large birefringence signal preceding contraction in single fwitch fibres of the frog. J. Physiol. 264: 141

5. Baylor, S. M. and Oetliker, H. 1976. The optical properties of birefringence signals from single muscle fibres. J. Physiol. 264, 164

6. Baylor, S. M. and Oetliker, H. 1976. Briefringence signals from surface and T-system membranes of frog. single muscle fibres, 264, 199

4. Other Research Activities

A. Viscoelastic properties of polyphosphozene

B. Mechanics of high performance fibers

C. Fatigue of polymeric fibers

D. Studies in wound strength

E. Studies in pulmonary vascular smooth muscle

III. Lay Summary

Research in high polymers, soft tissue, heart muscle, as well as smooth muscle are conducted in my laboratory. Computer controlled experimental systems covering both fast and slow mechanical phenomena are developed. Amongst various research projects, the cause of prolapse, a pathological condition prevalent in middle aged women, is under investigation and a optic probe which might aid cardiac infarct patients is developed.

IV. Publications

1. Abstracts published

Chen, H.Y.L., Ko, F.K., and Lundberg, J.L., "Polyaramide Fibers: Nonlinear Viscoelastic Behavior", The Second International Symposium for Artificial Organs, p. 4, September 1977.

Hart, R. T., Lee, J. L., Richardson, A. C., and Chen, H. Y. L., "Stress-Strain-History Relations of Human Endopelvic Fascia in Simple Elongation", Los Angeles California, ACEMB Proceedings, Vol. 30, p. 379, November 1977 (enclosed).

STRESS-STRAIN-HISTORY RELATIONS OF HUMAN ENDOPELVIC FASCIA IN SIMPLE ELONGATION

P2.18

R. T. Hart, J. L. Lee, A. C. Richardson, H. Y. L. Chen
School of Engineering Science and Mechanics
Georgia Institute of Technology

Pelvic relaxation is a general term used to describe all conditions in which the supporting structure in the female pelvis no longer maintains the pelvic organs in their normal position. This would include uterine prolapse, cystocele, rectocele, enterocele, and the various combinations of these.

The prevalent theory is that the pelvic fascia undergoes a generalized relaxation which results in a stretching or attenuation of the endopelvic supports. When the stretching becomes extensive and the fascia herniates, surgical repair is normally indicated. Accordingly, operative procedures have been devised to plicate and shorten the elongated fascia. But, despite the general improvement in operative techniques, the five year cure rate is disappointingly low.

During the past 5 years, 93 operations have been performed in the clinics of the third author, A. C. Richardson, which repaired demonstrable tears in the endopelvic fascia (not a general plication procedure) with an overall cure rate of over 95% [1]. Thus, it seems that the cause of pelvic relaxation is the localized failure or tearing of the endopelvic fascia and not a general attenuation of the fascia. After all, the term pelvic relaxation might be a misnomer. It should perhaps be replaced by the term pelvic support defects. To clarify the true cause of pelvic support defects, the following tasks are proposed:

(1) Identification of the pelvic supporting structure.

(2) Determination of the geometrical configuration of the supporting structure.

(3) Determination of the mechanical properties of the connective tissue composing the supporting structure.

(4) Determination of the loading conditions on the supporting structure.

(5) Structural analysis of the pelvic supports.

(6) Histological and biochemical studies of the connective tissue involved.

(7) Genesis of pelvic relaxation and its prevention.

As a pilot study, the identification of the pelvic supporting structure, determination of the geometrical configuration of these structures, and the histological and biochemical studies as well as mechanical studies of the connective tissue have been underway utilizing autopsy material.

Our anatomical studies have shown that there are several supporting structures in the pelvis, of which the endopelvic fascia is the major one. Histological studies have shown that endopelvic fascia has a large percentage (over 50%) of smooth muscle [2]. The mechanical behavior of endopelvic fascia specimens from two different locations will be reported here.

Tissue samples of endopelvic fascia were obtained from fresh autopsy material. A micro-computer controlled materials testing device, named Alphatron after Fung's constant α [3] was designed under the criteria of large stretch, small load, high resolution actuation, and continuously variable strain rate. The programmibility of the Alphatron allows us to perform various kinds of one-dimensional mechanical tests. As a preliminary study only simple elongation, stress-relaxation, and ultimate strength tests were performed.

Living soft tissue is anelastic and strongly nonlinear. Thus, we use a theoretical framework introduced by Fung [4] featuring a nonlinear viscoelastic model with a continuous relaxation spectrum and a quasi-linear relationship between stress history and strain history to describe the mechanical behavior. The data reduction scheme follows Chen and Fung [5].

A marked difference was found in the mechanical behavior of the two tissues specimens--one composed of dense regular connective tissue from the pelvic sidewall, the other composed largely of smooth muscle from the pubourethral ligament. Both tissues followed Fung's exponential law for simple elongation [3] but the dense regular tissue had a greater slope, α, than the ligament specimen. The stress relaxation data showed that the ligament specimen relaxed faster and took longer time to reach a plateau than the dense regular tissue. The ultimate strength of the two specimens was also different.

We have thus established a method of experimentation and data reduction to quantitatively observe the mechanical behavior of tissue specimens from different localities, histological composites, age, and case history. These studies together with the determination of geometrical configurations will enable us to eventually arrive at a structural analysis of pelvic supports.

Bibliography

1) Richardson, A.C., et.al., Am. J. of Ob. & Gyn., 126, 568-573, (1976).
2) Richardson, A.C., et.al., in press.
3) Fung, Y.C., Am. J. of Physiol., 213, 1532-1544, (1967).
4) Fung, Y.C., (ed), Biomechanics: Its Foundations and Objectives, Prentice-Hall, (1972).
5) Chen, Y.L., and Y.C. Fung, Biomechanics Symposium, 9-10, (1973).

Acknowledgements

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Discussions: please address to H.Y.L. Chen, School of Engineering Science and Mechanics, Georgia Institute of Technology, Atlanta, Georgia 30332.

IV. A. <u>Inventions and Discoveries</u>

1. Method for extrusion at high speeds based upon topological design of flow fields (with Dr. J. Lundberg, record of invention will be submitted upon request).

2. Optic Probe of the Electric Activity of Muscle. Recently, Pollack (1975) determined that the partially damaged ends of the heart muscle specimens produced an artifact which would cast doubt on the validity of all previous work. Experimental systems have been developed to avoid this artifact by optic means. Generally this is accomplished either by measuring a segment length between makers, e.g., Hefner's system, or by monitoring the sarcomere length with laser diffraction techniques, e.g., Pollack's system.

While working on the NSF grant ENG 75-10302, I encountered the same problems described above.

During design of an optical system to avoid the "damaged end" artifact, I saw that the laser light had been used in the sense of illumination and of Fourier waves. Continuing this line of thought, using laser light as an electromagnetic wave, I devised a technique to probe the electrical activity of muscle.

The theoretical background of the Optic Probe: As the laser beam passes through or scatters from muscle proper as a electromagnetic wave, the electric activities such as membrane polarization and cross bridge orientation will differentially retard the field propagation. Thus a polarized laser beam will be depolarized. The collected beam will pass through an analyzer and register on light detectors to give a resultant time intensity curve. The electric activity of muscle during the course of contraction then can be probed by the time course of the depolarization.

Clinical Application: In the case of open heart surgery for myocardial infarction, the infarcted regions are determined by x-ray angiography, and the regions of rigor (dead) myocardium as well as the rest (due to lack of oxygen) and active myocardium are by the inference or the guess of the surgeon. At NASA, AMES, Mirsky's group is developing a finite element method to pinpoint the infarcted region by spotting quantitatively the anomaly of the contraction, i.e., determining the three regions by mechanical observation, which is global. Dr. Chen's optic probe would pick up the optic signature of each region's electric activity, thus determining the regions directly and specifically. The feasibility of the probe as a clinical tool has been discussed with Dr. Robert Schlant, Dr. Don Nutter of Emory University, Dr. Brady of UCLA and Dr. Hefner of UAB, and received encouraging remarks.

The development of the probe is under way. The patent application will be processed, upon receiving release from NSF.

V. Research Grant Support

1. "Instrumentation and Experimentation in Heart-Muscle Mechanics", National Science Foundation ($38,200), September 1977 to March 1979.

2. "Studies on Wound Strength"(with Dr. A. C. Richardson, M.D.), American Cyanamid ($14,000), April 1978 to April 1979.

3. "Studies on the Viscoelastic Properties of Yarn", National Science Foundation ($5,000), October 1978 to June 1979.

VI. Brief Outline of Major Research Activity for the Year (July 1978 to June 1979).

1. Completion of the Heart Muscle System (July 1978 to December 1978).
2. Investigation on the functional dependence of the series element of myocardium on initial muscle length (January 1979 to June 1979).
3. Birefringence studies of muscle fibers: In light of kinetic theory of polymeric liquids to investigate the properties of cross bridges (July 1978 to June 1979).
4. Mechanics of soft tissues (July 1978 to June 1979).
5. Mechanics of high polymers (July 1978 to June 1979).